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PATENT SPECIFICATION

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(54) SLOW RELEASE FORMULATION

(71) We, MUNDIPHARMA A.G., a Swiss Corporation of Bahnhofstrasse 26, Rheinfelden, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to solid slow release preparations for oral administration and to a novel composition for the production of such slow release preparation.

It also particularly relates to preparations of the type referred to formulated as a solid dosage unit, in particular as a tablet or capsule.

It is known in the medical art to prepare preparations which then administered by the oral route provide for a delayed release of the active ingredient in the preparation, the object of such slow release preparations being either to ensure that release of the medicament does not take place until the preparation has reached a certain part in the alimentary tract and/or in addition to provide a controlled release of the medicament over a period of time so that a concentration of the medicament in the blood stream is maintained over a longer period than would be the case if the medicament was given other than in such a slow release formulation. Examples of slow release preparations include formulations such as enteric coated tablets and formulations in which the active ingredients are dispersed in a medium which is totally insoluble and where release of the medicament is brought about by break-down of the formulation due to mechanical means.

The object of the present invention is to provide an improved composition for the production of slow release preparations to be taken by the oral route, and preparations made from such compositions and containing active ingredients, which preparations have a number of advantages in use and are particularly suitable for maintaining a uniform continuous release of a medicament over a prolonged period of time. It is a particular object

of the invention to provide such solid dosage unit form in particular in tablet or capsule form, for prophylactic purposes, that is to say for the purpose of preventing a condition occurring as well as for the purpose of treating a condition when it arises.

We have found according to the invention that a mixture of a higher aliphatic alcohol and a water-soluble hydroxyalkyl cellulose provides a particularly suitable composition on which to base a slow release preparation.

According to one aspect of the invention, therefore, there is provided a solid slow release preparation for oral administration comprising an active ingredient incorporated in a matrix comprising a higher aliphatic alcohol as herein defined and a hydrated water soluble hydroxyalkyl cellulose.

The matrix comprising the higher aliphatic alcohol, as herein defined, and the hydrated water soluble hydroxyalkyl cellulose is a novel composition and according to a further aspect of the invention there is provided a composition of use in the production of slow release formulations comprising a matrix of said higher aliphatic alcohol and said hydrated water soluble hydroxyalkyl cellulose.

As explained more fully hereinafter the active ingredient in the preparation according to the invention may be incorporated in the matrix in a number of ways. Thus, it may be incorporated in the higher alcohol before this is blended with the hydroxyalkyl cellulose, or it may be incorporated in the hydroxyalkyl cellulose before this is incorporated in the higher alcohol. Also it may be incorporated in a partially or totally preformed blend of these two components or finally it may be included with a further excipient such as lactose which is then incorporated in the blend. Therefore according to a further feature of the invention there is provided a method for the production of a preparation according to the invention in which the active ingredient is incorporated in the alcohol or the hydroxyalkyl cellulose either before during or after the production of a blend thereof, if desired with addition of further additives, and at a

[Price 5]

convenient stage hydration of the hydroxyalkyl cellulose to the desired level is effected.

5 The preparation according to the invention, and the composition of use in the production of such preparation contains hydrated hydroxyalkyl cellulose. The hydration of the hydroxyalkyl cellulose is effected during the manufacture of the composition or of the preparation and has to be carried out carefully as
10 excessive hydration would result in an unmanageable granular mass whilst insufficient hydration of the hydroxyalkyl cellulose would result in an erratic and inferior release rate of medicament from the final tablet matrix.
15 The degree of hydration is in practice preferably that obtained by the addition of a quantity of water between twice and three times the dry weight of the hydroxyalkyl cellulose.

20 The term higher aliphatic alcohol as used herein means an aliphatic alcohol containing from 8 to 18 carbon atoms which may be substituted by a further aliphatic group also containing from 8—18 carbon atoms. A particularly preferred alcohol for use according to the invention is cetyl alcohol. Another preferred alcohol is cetostearyl alcohol which is an example of an alcohol containing a C_{18} — C_{19} aliphatic group substituent.

30 Lauryl alcohol, myristyl alcohol and stearyl alcohol may also be used. The hydroxyalkyl cellulose is preferably hydroxy ethyl cellulose, in particular that sold by Hercules Powder Company as Natrosol 250 (Natrosol is a
35 Registered Trade Mark).

Other hydroxyalkyl celluloses which may be used include hydroxypropyl and hydroxymethyl cellulose. The alkyl fragment of the hydroxyalkyl cellulose preferably therefore
40 contains from 1 to 4 carbon atoms.

In the compositions according to the invention the ratio of the higher aliphatic alcohol to the hydroxyalkyl cellulose determines, to a certain extent at least, the release rate of the medicament from the formulation. A
45 ratio of aliphatic alcohol to hydroxyalkyl cellulose (before hydration) of from 2:1 to 4:1 is preferred and a particularly preferred ratio is approximately 3:1. With this ratio a prolonged and uniform release of medicament is achieved. Thus for example a release period
50 of five hours can be achieved where the ratio of the higher aliphatic alcohol to the hydroxyalkyl cellulose is from 3:1.

55 As indicated above the preparation according to the invention is preferably shaped into a solid dosage unit or field into a capsule. Thus tablets and capsules are preferred formulations. When it is desired to prepare
60 tablets containing the slow release composition, then it is preferred to utilize an inert diluent such as lactose or talc, to achieve the appropriate concentration of slow release composition within said unit dosage form.
65 Such other ingredients as tablet binders,

granulating aids, colours, and flavouring materials as are well known to the tableting art may also be included in the finished formulation. A granulation mixture is prepared and compressed into tablets of suitable
70 size and shape, containing the desired quantity of sustained slow release composition to achieve a slow release of the active ingredient over a predetermined time period.

75 Slow release capsules may be prepared by filling the appropriate quantity of the above described tablet granulation mixture into gelatin capsules of suitable size and shape. Such modification of the tablet formulation as deemed necessary as for example the elimination of the table lubricant or the tablet binder, may be accomplished without effecting the slow release properties of the resultant capsule. Moreover, the preparation of a tablet granulation mix may not be required, in certain circumstances, to prepare slow release capsules. Thus, a slow release capsule may contain the mixture of the appropriate quantity of the combination of higher aliphatic alcohol and hydrated hydroxyalkyl cellulose, as herein described, together with an active ingredient and diluent. The diluent is necessary to achieve the appropriate concentration of the slow release composition within the unit dosage form. As for the slow release
85 tablet preparations, the time span for the release of the active ingredient in the capsule formulation will depend upon the concentration of the slow release composition within the total weight of the capsule formulation. Thus, when the capsule formulation contains 20 percent by weight of the new slow release composition, then the active ingredient will be released over a period of five hours, but when this concentration is increased to 25 percent by weight the span of
90 release of the active ingredient is increased to 6 to 7 hours and when the concentration of the slow release composition is 30 percent by weight of the formulation, then the span time for the release of the active ingredient will be nine to ten hours.

When it is desired to utilize the aforesaid slow release composition in therapy in the dosage form of sustained slow release tablets or capsules then the frequency of unit dosage administration will vary with the properties of the active ingredient selected as well as the individual patient's requirements. Thus a compound intended to provide a slow release
100 of a hypnotic agent will preferably be administered once, at bedtime, whereas a psychotropic mood elevating compound will be administered upon arising. A compound intended to produce bronchodilation or peripheral vasodilation may be administered at suitable intervals throughout the day.

In a similar manner, the duration of the slow release period selected will depend upon the nature of the active ingredient used and
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- the entity being treated. A preparation intended to be administered during the waking hours will commonly have two doses spaced at five hour intervals whereas a preparation intended to be used for sustained 24 hour therapy may have three doses spaced about eight hours apart. In practice, the particular therapeutic requirements will determine the selected proportion to be used.
- 10 A special advantage of the present sustained acting medications is that it now permits the administration of medicinals to animals during veterinary medical practice. Here the problems of administering a solid dosage form are such as to make the procedure most difficult and therefore, short-acting medications requiring frequent administration are avoided. The use of the above described sustained acting dosage forms results in an improved therapeutic armory in the treatment of veterinary disease.
- 20 The following Examples illustrate the invention:
- EXAMPLE I**
- 25 A tablet formulation containing as active ingredient nitroglycerin as prophylactic against angina pectoris is as follows.
- | | | | |
|----|--|-----------|--|
| | Cetyl alcohol | 15.0% w/w | |
| | Lactose | 45.5% w/w | |
| 30 | Hydroxy ethyl cellulose | 5.0% w/w | |
| | Talc | 15.0% w/w | |
| | Water | 14.0% w/w | |
| | Nitroglycerin Powder | | |
| | (Blend 1 part nitroglycerin 10 parts of lactose) | 16.0% w/w | |
| 35 | Talc | 2.5% w/w | |
| | Magnesium stearate | 1.0% w/w | |
- The tablet is manufactured as follows:
- Step 1
- 40 Melt the cetyl alcohol down in a water jacketed tank fitted with a stirring. Add the lactose, granulate the free flowing mass through a No. 16 stainless steel screen.
- Step 2
- 45 To the water in a peerless mixer fitted with shield paddle add the hydroxy ethyl cellulose. Stir until a granular paste is obtained.
- Step 3
- 50 Add the granules from Step 1 to the paste. Continue blending. Add the talc and nitroglycerin powder. Blend until a uniform granular mass is obtained.
- Step 4
- 55 The granules are then dried in a fluid bed or other suitable drier at 45°C for 30 minutes.
- After drying granulate through a No. 16 screen.
- Step 5
- Add the lubricants (magnesium stearate and talc) and compress. 60
- Compression Data:
- Tablet Weight is 400 mg.
- Punch size 13/32nd inch. Flat bevelled edge. 65
- Strength 6.4 mg. nitroglycerin content per tablet.
- With such a formulation the release of nitroglycerin from the matrix when tested in-vitro extends over a period of 5 hours. 70
- Such a release occurs as follows:
- | After | Release of nitroglycerin percentage | |
|--|-------------------------------------|----|
| 1 hour in artificial Gastric media | 8% | 75 |
| 2 hours in artificial pancreatic media | 17% | |
| 3 hours in artificial pancreatic media | 20% | 80 |
| 4 hours in artificial pancreatic media | 30% | |
| 5 hours in artificial pancreatic media | 25% | |
- From Example 1, the total concentration of alcohol and the cellulose derivative in the formulation is 20% by weight. It is a feature of this invention that when the amount of the alcohol and the cellulose derivative in the composition amounts to 20% and the ratio of these components is 3:1 then the slow release effect is achieved is the same as if the composition has a total amount of alcohol of 45%. It is a fact therefore that the effect of the cetyl alcohol and the cellulose derivative is to some extent more than additive, in other words the use of the hydrated hydroxy alkyl cellulose in combination with the aliphatic alcohol potentiates the effect of the aliphatic alcohol as an agent for producing slow release of the active ingredient. 85
- In the composition according to the invention where the ratio of alcohol to the hydrated hydroxy alkyl cellulose is 3:1 respectively and where both items in the composition constitute 25% by weight of the formulation the release rate of medicament from the formulation extends over a period of 6-7 hours. 90
- Such a composition is illustrated by the following Example. 95
- EXAMPLE II**
- A tablet formulation containing as active ingredient nitroglycerin as prophylactic agent against agina pectoris is as follows: 100
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	Cetyl alcohol	18.75% w/w	tained. Allow the mass to cool and granulate through a No. 16 stainless steel screen.	60
	Lactose	40.50% w/w		
	Hydroxy ethyl cellulose	6.25% w/w		
	Talc	15.00% w/w	Step 5	
5	Water	17.50% w/w	Lubricate the granules with talc and compress.	
	Nitroglycerin 1:10	16.00% w/w		
	Talc	2.50% w/w		
	Magnesium stearate	1.00% w/w		

EXAMPLE III

10 If Example I is repeated but with the ratio of alcohol to the hydrated hydroxy alkyl cellulose still 3:1 respectively but where both components now constitute 30% by weight of the formulation the release rate of active medicament now extends over a period of 9—10 hours.

15 As indicated above, the active ingredient may be included directly within, either the hydrated hydroxy alkyl cellulose or the alcohol melt.

20 The following Example illustrates the inclusion of an active medicament within the hydrated cellulose portion of the formulation. The active medicament in this instance is 25 potassium chloride which is formulated in a slow release matrix to avoid gastric irritation.

EXAMPLE IV

30 A slow release tablet formulation containing as active ingredient potassium chloride indicated whenever there is hypokalemia.

	Cetyl alcohol	14.00% w/w
	Potassium chloride	80.00% w/w
	Hydroxy ethyl cellulose	4.50% w/w
35	Water	10.00% w/w
	Talc	1.50% w/w

Manufacturing Procedure

Step 1
40 To the water at 50°C, contained in a "Peerless" mixer, fitted with shield paddle add the hydroxy ethyl cellulose. Blend until a uniformly hydrated granular mass is formed.

Step 2
45 Add to the cellulose granules, with constant stirring the potassium chloride. Continue mixing until a free flowing uniform granule blend is obtained.

Step 3
50 Dry the cellulose/potassium chloride granules in a fluid bed drier for 30 minutes at 50°C. Granulate the dried granules through a No. 16 stainless steel screen.

Step 4
55 Melt the cetyl alcohol down in a water jacketed tank fitted with an efficient stirrer. Hold the melt at 60—70°C and incorporate the granules from step 3. Continue stirring until a free flowing granular mass is ob-

Core Compression Data

Core weight	750.0 mg.	65
Punch size	7/16th inch. Deep Concave	
Disintegration	4—6 hours	

Step 6

The cores are then pan coated using normal coating techniques.

70 With such a formulation, the release of potassium chloride from the matrix when tested in vitro extends over a period of 5 hours. Such a release occurs as follows.

After	Release of Potassium Chloride percentage	
1 hour in Artificial Gastric Media	40.1	80
2 hours (in Artificial Pancreatic Media)	61.0	
3 hours (in Artificial Pancreatic Media)	77.4	
4 hours (in Artificial Pancreatic Media)	90.4	85
5 hours (in Artificial Pancreatic Media)	100.0	

The following Examples serve to illustrate the varying methods of manufacturing of the 90 slow release preparations.

In this instance the active medicament is Aminophylline, intended to relax involuntary muscle and relieve bronchospasm, and is included directly within the cetyl alcohol melt; 95 the resultant granules are then intimately included within the hydrated cellulosic granular mass.

EXAMPLE V

Aminophylline	75.42% w/w	100
Cetyl alcohol	16.76% w/w	
Hydroxy ethyl cellulose	5.02% w/w	
Water	15.50% w/w	
Talc	1.6% w/w	
Magnesium stearate	0.6% w/w	105
F. D. & C. (Food, Drug & Cosmetic) Yellow 5 lake	0.1% w/w	
Saccharine sodium	0.5% w/w	

Manufacturing Procedure

Step 1
110 Melt the cetyl alcohol down in a water jacketed tank. Hold the cetyl melt at 60°C and incorporate with stirring the aminophylline. Granulate the mass so obtained through

- a No. 16 sieve. Harden the granules so obtained by fluid bed drying at room temperature.
- Step 2**
5 Prepare the hydroxyethyl cellulose mix in a Peerless mixer with shield paddle using water at 70°C. Incorporate the blend from Step 1. Total blending time 3 hours.
- Step 3**
10 Dry the granular mass from Step 2 at 40°C using a fluid bed drier. Granulate through a No. 16 sieve.
- Step 4**
15 Lubricate the granules incorporate the colourant and saccharine sodium and compress.
- Compression Data**
- | | |
|------------------|---------------------|
| Weight of tablet | 596.60 mg. |
| Punch size | 15/32nd inch Normal |
| | Concave |
| Disintegration | 5 hours release |
- 20
- With such a formulation the release of aminophylline from the matrix when tested in vitro extends for the designed period of 5 hours. Such a release occurs as follows.
- 25
- | After | Release of aminophylline percentage |
|---|-------------------------------------|
| 1 hour (in artificial gastric media) | 28.0% |
| 2 hours (in artificial pancreatic media) | 49.8% |
| 3 hours (in artificial pancreatic media) | 67.0% |
| 35 4 hours (in artificial pancreatic media) | 83.0% |
| 5 hours (in artificial pancreatic media) | 100.0% |
- 40 This particular formulation has been subjected to in vivo appraisal on five young, healthy individuals. The following data was recorded in order to ascertain the efficacy of 5 hour in vitro release model.
- Subjects**
45 The tests were carried out on five young, healthy individuals. Normal food intake was maintained for the duration of the experiment, and no gastric irritation was recorded.
- Dosage and Sampling**
50 One × 450 mg. slow release tablet was administered to each subject at times 0 hours, 12 hours and 24 hours.
- A premedication blood sample was initially taken to serve as a blank, and a further eleven samples were taken at intervals during the
- nine hour period after ingestion of the first and third doses.
- The sample withdrawn, (18 mls.) was added to 3.8% w/v sodium citrate (2 ml.), the red blood cells were spun down, and 6 ml. of citrated plasma was removed by pipette. Prior to analysis these plasma specimens were kept at 4°C. 60
- Analytical Method**
The procedure used was essentially that of J. A. Schack and S. H. Waxler (1949), J. Pharmacol, 97, 283 involving a single organic extraction with a chloroform - propan - 2 - ol mixture, and a subsequent re-extraction with dilute alkali. The ultraviolet absorption of the theophylline molecule was determined. 70
- The mean results obtained from the investigation are recorded in the Table below.
- | Time (hours from 1st dose) | mg. theophylline per ml. whole blood |
|----------------------------|--------------------------------------|
| 1st dose 0.0 | — |
| 1.50 | 3.2 |
| 3.25 | 6.0 |
| 5.50 | 6.2 |
| 7.00 | 6.0 |
| 8.50 | 5.9 |
| 2nd dose 12.00 | — |
| 3rd dose 24.00 | 2.3 |
| 25.50 | 6.0 |
| 27.25 | 7.0 |
| 29.45 | 6.5 |
| 31.00 | 6.0 |
| 32.50 | 5.2 |
| 36.00 | 3.8 |
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- 90 From this in-vivo appraisal it was observed that (a) in no instance was gastric irritation recorded, (b) the idealised flat plasma concentration curve, significant of a satisfactory slow release formulation, has almost been attained. (c) the incidence of drug accumulation has been avoided. (d) the desired levels of 6 mcg. theophylline per ml. whole blood, reported to relieve bronchospasm (Schack & Waxler), has been realised.
- The following preparation serves to illustrate an example where the active medicament can be incorporated into either the hydrated cellulosic ingredient before this is incorporated into the higher alcohol, or it may be incorporated in the higher alcohol before this blended with the hydrated hydroxy alkyl cellulose. 100
- EXAMPLE VI**
- A tablet formulation containing as active ingredient papaverine hydrochloride indicated for relaxation of involuntary muscle. 110
- | | |
|--------------------------|-------------|
| Papaverine hydrochloride | 74.0% w/w |
| Hydroxy ethyl cellulose | 6.0% w/w |
| Water | (16.0% w/w) |
| Cetyl alcohol | 18.0% w/w |
| Talc | 1.5% w/w |
| Magnesium stearate | 0.5% w/w |
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	Manufacturing Procedure—Method 1	Manufacturing Procedure—Method 2	55
	Step 1	(alternative)	
	To the water at 50°C, contained in a Peerless Mixer, add the hydroxyethyl cellulose.	Step 1	
5	Blend until a uniformly hydrated mass is obtained.	Melt the cetyl alcohol down, in a suitable tank fitted with an efficient paddle. Hold the melt at 60°C and incorporate the finally sieved papaverine hydrochloride. Mix thoroughly until a free flowing granular blend is obtained.	60
	Step 2	Step 2	
10	Add to the hydrated cellulose mass the papaverine hydrochloride. Continue mixing until a free flowing uniform granule blend is obtained.	Pass the material from step 1 through a No. 20 stainless steel screen.	65
	Step 3	Step 3	
15	Granulate the mass obtained through a No. 16 stainless steel screen. Dry the crude granules at 60°C for 45 minutes in a fluid bed drier. Granulate the dried granules through a No. 20 stainless steel screen.	To the water at 50°C contained in the "Peerless" mixer add the hydroxy ethyl cellulose and blend until a uniformly hydrated cellulose granule is obtained.	70
	Step 4	Step 4	
20	Melt the Cetyl alcohol in a water jacketed tank fitted with an efficient stirrer. Hold the melt at 60°C and incorporate the granules from step 3. Continue mixing until a free flowing granular mass is obtained.	Add the granules from step 2 to the hydrated cellulosic material. Intimately blend, until a free flowing granule is formed.	
25	Allow the mass to cool to room temperature before passing through a No. 20 stainless steel screen.	Step 5	75
	Step 5	Dry the granules at 40°C for 60 minutes. Granulate through a No. 16 stainless steel screen. Again dry the granules at 60°C for a further 30 minutes before passing through a No. 20 stainless steel screen.	80
	Lubricate the granules with talc and magnesium stearate and compress.	Step 6	
		Lubricate and compress the granules.	
30	Compression Data	Compression Data	
	Tablet weight 202.2 mg.	Tablet weight 202.2 mg.	
	Punch size 5/16th inch F.B.E.	Punch size 5/16th inch F.B.E.	85
	Disintegration 5 hours	Disintegration 5 hours. Percentage release as for method I.	
35	Papaverine hydrochloride content 150 mg. per tablet	Papaverine hydrochloride content 150 mg. per tablet	90
	With such a formulation, the release of papaverine hydrochloride from the matrix when tested in-vitro extends over the designed period of 5 hours.	If Example VI is repeated and with the ratio of alcohol to hydrated hydroxy alkyl cellulose remaining at 3:1 respectively but where both components now constitute 30% by weight of the formulation the release rate of active medicament from the matrix now extends over a period of 7—8 hours.	95
40	Such a release occurs as follows.	This final Example illustrates a further approach to formulation procedure essentially pertinent to active medicaments of a hydrophobic nature.	100
		It is a feature of this invention that the hydroxy alkyl cellulose is sufficiently hydrated. Also that an intimate blend be obtained between the active medicament and the hydrated cellulose. When dealing with active medicaments of a pronounced hydrophobic nature two approaches exemplified below can be adopted.	105
	After		
45	1 hour (in Artificial Gastric Media)	Release of papaverine hydrochloride percentage	
	2 hours (in Artificial Pancreatic Media)	27.5	
	3 hours (in Artificial Pancreatic Media)	52.0	
50	4 hours (in Artificial Pancreatic Media)	72.2	
	5 hours (in Artificial Pancreatic Media)	88.1	
		100.0	

EXAMPLE VII

A tablet formulation containing as active ingredient quinidine polygalacturonate indicated in the control of the cardiac arrhythmias

5	Quinidine polygalacturonate	76.4%
	Hydroxy ethyl cellulose	7.0%
	Water	(55.0%)
	Cetostearyl alcohol	14.0%
	Talc	1.6%
10	Magnesium Stearate	1.0%

Manufacturing Process—Method 1

Step 1

Blend the hydroxy ethyl cellulose with the quinidine polygalacturonate then add to the bowl of the "Peerless" mixer.

Step 2

Add the water and blend until a granular material is obtained.

Step 3

If necessary part dry the moist mass, at 70°C for ½ hour, and then pass through a 16 stainless steel screen. Total drying time 1 hour at 70°C in a fluid bed drier.

Step 4

Pass the dry granules through a 20 stainless steel screen. Melt the cetostearyl alcohol and then incorporate the granules from step 4. Mix thoroughly, allow to cool, and pass the mass through a 20 stainless steel screen.

Step 5

Lubricate and compress.

Compression Data

	Tablet weight	360.0 mg.
	Punch size	13/32nd inch F.B.E.
35	Distinguation	6 hours
	Quinidine polygalacturonate content	275.0 mg.

Manufacturing Procedure—Method 2

With the alternative method, utilising the same ingredients, as above, and in the same quantities, the active medicament is suitably and thoroughly wetted by direct administration of the water. The moistened material is then used in turn to hydrate the cellulose.

Step 1

Add the water at 50°C, to the quinidine polygalacturonate in the bowl of the Peerless mixer. Blend until a uniformly moistened mass is obtained.

Step 2

To this moist mass add the hydroxy ethyl cellulose. Blend for 1—1½ hours. A free flowing cellulose granule is obtained.

Step 3

If necessary part dry the mass at 70°C

for 30 minutes in a fluid bed drier and then pass through a No. 16 stainless steel screen. Further dry the crude granules at 70°C for 1 hour in a fluid bed drier. Pass the dried granules through a No. 20 stainless steel screen.

Step 4

Melt the cetyl alcohol down a suitable vessel and hold the melt at 60°C. Add the granules from step 3 and blend until a free flowing granular mass is obtained. Cool to room temperature and granulate through a No. 20 stainless steel screen.

Step 5

Lubricate and compress.

Compression Data

	Tablet weight	360.0 mg.
	Punch size	13/32nd inch F.B.E.
	Distinguation	6 hours
75	Quinidine polygalacturonate content	275.0 mg.

With such a formulation the release of quinidine polygalacturonate from the matrix, when tested in vitro extends over the desired period of 6 hours.

WHAT WE CLAIM IS:—

1. A solid slow release preparation for oral administration comprising an active ingredient incorporated in a matrix comprising a higher aliphatic alcohol as herein defined and a hydrated water soluble hydroxy alkyl cellulose.

2. A preparation as claimed in claim 1 in which the degree of hydration of the hydroxy-alkyl cellulose is that produced by the addition of water to the extent of two to three times that of the dry weight of the hydroxy-alkyl cellulose.

3. A preparation as claimed in claim 1 or claim 2 in which the active ingredient is nitroglycerin, potassium chloride, aminophylline or papaverine hydrochloride.

4. A preparation as claimed in claim 1 substantially as herein described with reference to any of Examples I—V.

5. A preparation as claimed in claim 1 substantially as herein described with reference to Examples VI and VII.

6. A method for the production of a preparation claimed in claim 1 in which the active ingredient is incorporated in the alcohol or the hydroxy-alkyl cellulose either before during or after the production of a blend thereof, if desired with addition of further additives, and at a convenient stage hydration of the hydroxyalkyl cellulose to the desired level is effected.

7. A method as claimed in claim 6 substantially as herein described with reference to any of Examples I to V.

8. A method as claimed in claim 6 sub-

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- stantially as herein described with reference to Examples VI to VII.
9. A preparation as claimed in claim 1 when prepared by a process as claimed in claim 6 or claim 7.
10. A preparation as claimed in claim 1 when prepared by a process as claimed in claim 8.
11. A method of preparing a formulation in solid dosage unit form which comprises shaping a preparation as claimed in any of claims 1 to 5 or 9 into a solid dosage unit or filling said preparation into a capsule.
12. A method as claimed in claim 11 in which the preparation is shaped into a tablet.
13. A method as claimed in claim 11 substantially as herein described with reference to Examples I—IV.
14. A method as claimed in claim 11 or claim 12 in which a preparation as claimed in claim 10 is used.
15. A method as claimed in claim 14 substantially as herein described with reference to Example VI or VII.
16. A formulation in solid dosage unit form, in particular as a tablet or capsule when made by a method as claimed in claim 12 or claim 14.
17. A formulation as claimed in claim 16 when made by a method as claimed in claim 15.
18. A matrix for use in the production of slow release formulations comprising an intimate mixture of a higher aliphatic alcohol as herein defined and a water soluble hydroxyalkyl cellulose hydrated to that extent which is produced by the addition of water between two and three times that of the dry weight of the hydroxyalkyl cellulose.
19. A matrix composition as claimed in claim 18 in which the ratio of the alcohol to the hydroxyalkyl cellulose is from 2:1 to 4:1 by weight.
20. A matrix as claimed in claim 19 in which the ratio of alcohol to hydroxyalkyl cellulose is 3:1 by weight.
21. A matrix as claimed in any of claims 18 to 20 in which the alcohol is cetyl alcohol.
22. A matrix as claimed in any of claims 17 to 21 in which the hydroxyalkyl cellulose is an hydroxyethyl cellulose.

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